

(4822) Churchill		Review: clinical features	
(4956) Overholt & Schmidt	721 gender?		early diagnosis
<u>Michigan</u>			
(3756) Brines & Kenning	63M; 5F		17 Polish, 5 Russians, 4 Austrians, 4 Yugoslavs
(4046) Hammond	32M; 8F		early diagnosis
(4813) Ballantine & Byron	1M		cerebral metastasis
(4816) Black	1M		cardiac metastasis
(4847) Levitt	85M; 15F		exploratory surgery
<u>Minnesota</u>			
(4068) Olds & Kirklin	162M; 44F		92 squamous, 111 adeno- carcinoma, 3 mixed
(4069) Olds	(same)		
(4144) Harrington		Review: surgical management	
(4145) Harrington		Review: pneumonectomy	
(4169) Simons		Review: etiology	
(4272) Harrington		Review: pneumonectomy	
(4345) Kinsella	1M		five-year cure
(4351) Moersach & Tinney	370M; 78F		45% adenocarcinoma, 52% squamous
(4352) Moersach & Tinney		Review: early diagnosis	
(4421) Brindley	34M; 11F		surgical treatment
(4425) Clagett & Brindley	(same)		surgical prognosis
(4442) Harrington		Review: pneumonectomy	
(4460) Moersach		Review: diagnosis	
(4477) Tinney		"cigarette cough"	
(4523) Fair & Clagett	1M; 1F		surgical treatment
(4538) Ikeda		Review: alveolar cell tumor	
(4548) McDonald et al	17M; 6F		hematoma
(4566) Samper & Clagett	1M		actinomyces tongue
(4768) Mandell		Review: clinical	
(4832) Good	6M		early diagnosis
(4951) McDonald & Woolner		Review: sputum cytology	
<u>Missouri</u>			
(3665) Glenn		Review: clinical features	
(4129) Bondurant	1M		negro
(4271) Womack & Graham	3M; 1F		developmental
abnormalities			
(4528) Goldman	1M		pneumonectomy
(4529) Graham & Womack		Review: differential diagnosis	
(4740) Graham		Review: surgical treatment	
(4815) Bergmann et al	3M	coffee peddler	differential diagnosis
(4915) Ackerman		Review: diagnosis	
(4936) Goldman	1M		pleural effusion
(4937) Graham		Review: surgery	

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Nebraska

(4128) Bisgard	1M	farmer	pneumonectomy
(4784) Simonds & Anderson		Review: treatment	

New Jersey

(3553) Dieffenbach		Review: clinical features	
(4028) Casilli & White	2M; 1F	dogbreeder, postmaster	bronchial adenoma

New York

(2959) Karnah & Cracovaner	1F		bronchoscopy
(3047) Martin & Ellis	5 gender?		needle biopsy
(3341) Kernan	4M; 4F		radon implantation
(3670) Wasch & Epstein	39M; 15F		roentgenologic classification
(4023) Biederman	2M	bricklayer, window cleaner	
(4032) Craver	175 gender?		sputum cytology
(4075) Rabinovitch et al	40 gender?		4 squamous, 31 cylindrical, 17 undifferentiated, 14 adenocarcinoma
(4124) Bereston & Mey	1M; 1F		osteomyelitis
(4151) La Fuente & Palacios	1M	waiter	tuberculosis
(4161) Ornstein & Epstein	26 gender?		classification
(4171) Thompson		Review: surgical treatment	
(4173) Ulsar & Auerbach	1M*	watchman, ex-smoker	Russian
(4270) Wessler & Rabin	36 gender?		neurological complications
(4273) Neuhof	5M; 2F		pneumonectomy
(4353) Murray		Review: clinical features	
(4362) Stout	20 gender?		bronchial adenoma
(4368) Wood	1F	housemaid	adenomatosis
(4458) Mitton & Hardisty	88M; 12F		diagnosis
(4516) Chamberlain & Gordon	5M; 5F		
(4647) Neuhof	1M; 1F		cylindroma
(4713) Aufses	1F		slow growth
(4747) Hankin	32M; 4F		metastases
(4754) Humphreys	106M* 16F		42 operable, 29 resectable
(4863) Neuhof & Aufses	52 gender?		pneumonectomy
(4883) Silverman & Angrist	2F		adenocarcinoma
(4916) Auerbach	46M; 4F		grouping by location
(4938) Hayes		Review: symptomatology	

North Carolina

(4259) Seay	8M; 1F		irritation theory
(4819) Bradshaw		Review: etiology and clinical features	

Ohio

(4038) Freedlander & Wolpaw	3M; 1F		differential diagnosis
(4052) Jones et al	13 gender?		surgical exploration
(4125) Berghausen	6M	laborer, hatter, mechanic manufacturer, night watchman	clinical reports

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(4226) Freedlander & Greenfield	2F		metastatic cancer
(4343) Johnson & Reinhart	57M; 9F		necropsies
(4344) Karsner	1M		nasal metastases
<u>Oklahoma</u>			
(4131) Chont	1M	farmer	bronchial asthma
(4929) Fair		Review: surgical treatment	
<u>Oregon</u>			
(4552) Moore	2M; 2F		bronchial asthma
(4718) Berg et al	65M*	4 nonsmokers	
<u>Pennsylvania</u>			
(4029) Chamberlain	2M; 1F		differential diagnosis
(4060) Nahor & Staderman	30M	occupation not important	necropsies
(4227) Freedman & Bosse	1F		multifocal cancer
(4253) Parrone & Levinson	95M* 20F	1 nonsmoker	no negroes
(4342) Johnson	16M; 4F		pneumonectomy
(4436) Freedman et al	23M; 7F		early diagnosis
(4469) Schnabel		Review: clinical features	
(4554) Muller & Miller	67 gender?		surgical treatment
(4615) Clerf & Herbut	303M; 33F		bronchoscopic diagnosis
(4632) Herbut & Clerf	38 gender?		bronchoscopic cytology
(4633) Herbut & Watson	16M; 1F		Pancoast syndrome
(4831) Gibbon et al	50M; 6F		surgical exploration
(4865) Norris	310 gender?		bronchoscopic diagnosis
(4866) O'Keefe	131 gender?		delayed diagnosis
(4920) Burnett et al	67 gender?		post pneumonectomy
(4922) Clerf & Herbut		Review: bronchospic diagnosis	
(4962) Ryan & Meyer	111M	pathologic classification	
<u>South Carolina</u>			
(4096) Coleman	18 gender?		pneumonectomy
<u>Tennessee</u>			
(4241) Johnson & Daniel		Review: clinical features	
(4256) Quinland	3M	machinist	negroes
<u>Texas</u>			
(4047) Hanks		Review: etiology	
(4095) Tripoli & Holland	171M; 24F		needle puncture biopsy
(4135) Diamond	20 gender?		clinical diagnosis
(4364) Wallace & Jackson	26M* 2F	8 heavy smokers, 6 moderate, 1 nonsmoker, 12 no data	
(4876) Quick & Brindley	44M; 4F	"cigarette cough"	negroes
(4955) Moyer & Ackerman		Review: clinical features	
(4974) Wallace		Review: cytologic diagnosis	

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Virginia

(4049) Higgins -	25M; 5F	Review: etiology	
(4724) Coleman	79M; 9F		surgical treatment
(4725) Coleman	6M; 1F	farmer, painter	surgical treatment
(4952) Hank & Myer	5M; 1F	truck driver, coal miner	histochemical lipase
		farmer, locomotive fireman	

Washington

(4146) Hershberger	16M*	12 smokers	
		10 alcohol drinkers	

Wisconsin

(2734) Ochaner & Nesbit	1M		pulmonary abscess
(3656) Rice	18M; 12F	8 housewives, 4 laborers	
		3 farmers, 3 metal workers	
		1 locomotive fireman	
(4829) Gale & Curreri		Review: surgical indications	

Australia

(3638) Harvey	87M; 13F		38 exposed to noxious inhalation
		25 outdoors	
(4077) Robb	1M		Russian Jew
(4269) White	1M		traumatic pneumothorax

Canada

(4031) Corbett	2M		diagnosis
(4175) Whiteside		1F	pneumectomy
(4783) Simon	1M		alveolar cell cancer
(4858) Nadore	72 gender?		15 squamous, 6 adeno-carcinoma, 35 undifferentiated

China

(4050) Esieh et al	14M; 7F	cook, peanut peddler, clerk, railway employee, merchant, physician, farmer	clinical reports
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Denmark

(4434) Engelbreth-Holm	7M; 5F		bronchial adenoma
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Great Britain

(4078) Roberts		Review: treatment	
(4139) Foster-Carter	12M; 10F		bronchial adenoma
(4157) Mason		Review: clinical features	
(4223) Chandler		Review: clinical features	
(4257) Robertson	12M; 10F		clinical features
(4329) Davidson		Review: differential diagnosis	
(4336) Barnett	69M* 18F	404 male smokers, 334 female smokers	

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(4355) Barnard			Review: pathologic features	
(4359) Smart			Review: clinical features	
(4360) Stewart & Allison		1F		bronchiectases
(4431) Dormer et al	1M			Pancoast tumor
(4445) James & Pagel	2M			Pancoast tumor
(4782) Sellors et al	130 gender?			surgical treatment
(4820) Brock	101 gender?			surgical treatment
(4950) Mason	902M; 98F			38t male epidermoid, 11t female epidermoid
<u>Italy</u>				
(4168) Guarnerio & Cambria	9M			differential diagnosis
<u>Japan</u>				
(4065) Murakami	1M			roentgen diagnosis
<u>New Zealand</u>				
(4225) Cronin	1M		motor engineer	case report
<u>Russia</u>				
(4137) Farberov & Baslow	12M; 9F			roentgen therapy
(4656) Shik	116M; 22F			15.6t of all cancer

* Smoking habits recorded

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Questionable Increase Incidence in Lung Cancer

The debate as to whether the increase in lung cancer incidence was real, apparent, or both, continued during the 1940's. The most informative literature review was by Willis in his monograph entitled *Pathology of Tumours*:

"Whereas up to the second decade of this century, carcinoma of the lung was regarded as a relatively rare disease, it is now recognized as one of the commonest forms of cancer, accounting for between 5 and 15 per cent of cases of carcinoma in most recent necropsy series. Is the increase real or only apparent? Attempts to answer this question have reached contradictory conclusions. Having read many of the contributions to the controversy, and having surveyed my own experience on the diagnostic errors made in this disease, my opinion is that it is not possible either to affirm or to deny that there has been a real increase. My reasons for this non-committal opinion are briefly as follow:

(a) Clinical misdiagnoses, even with all modern diagnostic facilities, are still made in a high proportion of cases. Between 1931 and 1944 I performed 84 necropsies on cases of pulmonary carcinoma, all in a major general hospital; of these, 35 (42 per cent) had been misdiagnosed, 19 as some other kind of malignant disease and 16 as non-neoplastic diseases. Clearly then, the mortality statistics of lung cancer are of dubious value.

(b) Pathological misdiagnoses are still made in not a few cases, and until the last two decades they were very common. Let anyone who doubts this look up some of the standard pathological journals for the later decades of the nineteenth century, and study the many records of 'mediastinal sarcoma', 'lymphadenoma', 'pleural or pericardial endothelioma', etc. In the light of what we now know of the structure, spread and misleading symptomatology of bronchial carcinomas, the correct diagnosis of many of the cases so recorded will be plain. It is of course now well recognized that most of the erstwhile 'mediastinal oat-cell sarcomas' are secondary deposits of bronchial carcinoma. It is still not sufficiently recognized that secondary growths in the pericardium, pleura or cervical lymph glands may easily be mistaken for primary tumours; and that other errors of pathological diagnosis are being made by those who are unaware of the structural versatility of bronchial cancer and

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the ease with which small primary growths may escape detection at necropsy.

(c) Modern diagnostic methods, especially radiography and bronchoscopy, must have brought about, not only improved diagnosis of lung cancer, but an increasing general acquaintance with the disease and its behavior.

(d) Pulmonary carcinoma will, of course, have shared in the general increase of cancer because of the increased proportion of old people in the population. Comparison of early and recent necropsy series as regards the frequency of lung cancer have often failed to take account of the age compositions of the respective series. Since the disease is much commoner in men than in women, allowance must also be made for the sex ratios of necropsy series to be compared.

(e) Of significance are the analyses of necropsy records made by Bonser and by Passey and Holmes. Bonser's analysis of the necropsies during 41 years at Leeds, where an unusually high proportion of fatal cases were examined, showed no increase in the incidence of intra-thoracic cancer when considered with respect either to the total number of necropsies, the total number of cancer cases, or the total number of admissions to hospital. Passey and Holmes studied the incidence of intra-thoracic cancer in the necropsy records of 16 major teaching hospitals in Great Britain; in 8 hospitals there was no evidence that this was increasing, in 3 the results were inconclusive, while in 5 institutions which did show an increase there were special circumstances which may have been responsible. Sitsen and Steiner also are among the many pathologists who deny that there is any satisfactory evidence of a real increase in the incidence of lung cancer during recent years. The suspicion is that where such increase has appeared to have been conspicuous, there was formerly a low standard of accuracy of pathological diagnosis and that the standard has improved with the passage of time.

For the foregoing reasons, comparisons of early and recent clinical or necropsy estimates of incidence, or comparisons of the findings in different countries or in different hospitals, must be quite unreliable. So much depends on the personal experience of the clinicians and pathologists concerned, and current journals contain evidence enough that a uniformly high standard of diagnosis of this elusive disease has not yet been attained by either. Now that the properties of the disease are becoming better known, however, its true frequency and trend in a given community or institution

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thousand cases in Canada (4646); and Rosahn, based on 86 autopsies performed at Yale University School of Medicine (4079). The latter reviewed factors which might have been responsible for the increase such as improved clinical and pathologic methods of diagnosis, increased attention to lung cancer, increase in span of human life, and no comparable increase in tumors of the skin.

Boyd, a Professor of Pathology from the University of Toronto, reviewed the reasons for the recent increase in lung cancer. He suggested that the greater part of the increase was apparent and was not prepared to "go so far as to state that none of it is real."

"We have seen that the most important factor in the recent increased incidence of bronchial carcinoma is its better recognition. This is true for the clinician, radiologist and pathologist. The eyes of the first two have been opened by the observations of the pathologist. The latter has been misled in the past for three principal reasons. (1) It is easy to overlook the bronchial origin of the gross lesion, in which case the tumor is apt to be regarded as a metastatic one. (2) These tumors may closely mimic sarcomas and lymphosarcomas, and very many of the cases in the past have been wrongly labelled as such lesions. (3) The natural history of the disease as illustrated by the behavior of the metastases is highly characteristic, but the knowledge of this truth is of recent date. It is suggested that various factors which have been discussed coupled with the increase in the span of life are sufficient reason for the apparent increase in bronchial carcinoma." page 13, (4130)

Clinical Diagnosis and Treatment

As indicated in the Tabulated Case Reports, about one-quarter of articles were reviews on clinical features,

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differential diagnosis, surgical management, histopathologic classification, and radiation therapy. Surgeons such as Graham from Missouri, Ochsner from Louisiana, and Overholt from Massachusetts, were initially optimistic about pneumonectomy, but towards the late 1940's, it became apparent that the five-year survival rate was just as uncommon as radiation therapy.

There was consensus on the importance of early diagnosis. However, there were conflicting opinions as to whether delay in treatment was due to patients' or physicians' unawareness of signs and symptoms to assure early diagnosis. In a survey conducted by Bates & Ariel at Veteran's Hospital at Hines, Illinois, although 18 lung cancer patients were given definitive treatment, 5 favored to confer with their doctor within three months of onset and 14 cases were not provided treatment within 3 months of first visit, and 2 cases of delay decided by both patient and physician (4814). There was a necessity to educate the general public on early symptoms of lung cancer and to encourage physicians to exclude the disease in differential diagnosis of chest signs and symptoms. There were articles advising young physicians to improve history taking and physical examination for diagnosis of lung cancer (4897). There was no mention of cigarette smoking as a potential cause.

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C. CIGARETTE SMOKING AND LUNG CANCER

The literature on tobacco use and lung cancer became more specific during the 1940's. Unlike earlier decades, publications just prior to 1950 separated the health effects of cigarette smoking from those of pipe and cigar smoking and tobacco chewing. Characterization of smoking habit detailed only as far as whether the individual was a non-smoker or cigarette smoker, and occasionally a heavy smoker. The number of cigarettes consumed daily was rarely specified and the manner of inhaling cigarette smoke was not mentioned in medical publications.

Research on health effects of cigarette smoking was usually conducted by physicians. Prior to 1950, there was hardly any non-medically trained scientist who conducted health research because doctorates in biochemistry, physiology (and other medical sciences) were rare. Lung cancer research conducted by physician-researchers was criticized by those who had non-medical degrees, particularly, chemists, biologists, epidemiologists and public health workers. The publications discussed below were written mostly by physicians, except those under the subtopic of chemical constituents of cigarette smoke, contributed by chemists. Articles on composition of cigarette smoke published during the 1930's are transferred from Chapter III and included below together with those published during the 1940's.

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Lung Cancer Monographers

As stated in the Introductory List of Lung Cancer Monographers, Fried continued to question any causative role of tobacco: "Evidence thus far adduced is contrary to the idea that bronchiogenic cancer is caused by tobacco" (see above, pages 428 and 429 for detailed quotation (4801). Willis reviewed the role of carcinogenic hydrocarbons with special reference to tobacco smoke.

"Experimental investigation, has shown that the incidence of lung tumours in mice can be markedly increased by the administration of carcinogenic hydrocarbons by inhalation or by subcutaneous, intra-peritoneal or intravenous injections. The possibility must, then, be conceded that exposure of human beings to such substances may be a factor in the causation of lung cancer; and that, while inhalation is clearly the most likely mode of introduction of such agents, absorption by other routes must also be considered. Tar, oil, soots, tobacco smoke and other smokes, must all be arraigned; but clearly, proof of either the culpability or innocence of any particular material will not be easy to establish. Such proof will entail (a) demonstration of the presence of carcinogenic substances in the suspected material, (b) evidence that the material is inhaled or otherwise absorbed by exposed persons, and (c) evidence that habitually exposed persons do show an excessive incidence of lung cancer, and that this excessive incidence is reduced by eliminating the suspected risk. While the first step (a) has already been accomplished for many of the suspect materials, scarcely any of the evidence (b) or (c) has been obtained, and it will be very difficult to obtain.

For example, suppose that tobacco smoking is an important cause of lung cancer and that it acts by producing chemical carcinogens which are inhaled. It may be easy to identify the carcinogens in tobacco smoke or tar, but it may be difficult to prove that they are effectively inhaled, even more difficult to group patients correctly according to their present and past tobacco consumption, and probably impossible to prevail on any large group of men of homogeneous occupation to renounce smoking for life so that the ultimate incidence

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of lung cancer in them (proved by necropsy) may be compared with that of their smoking fellows. Comparisons of the smoking habits of victims of lung cancer with those of control cases obtained by careful questionnaires, like Muller's, afford strong grounds for suspecting the carcinogenic results of smoking; but, however strongly suggestive, they cannot afford incontrovertible proof - especially in the eyes of smokers themselves! Proof of the harmfulness of inhaled domestic and industrial soots and smokes or of dust from tarred roads, to which all persons in urban populations are almost equally exposed, will be even more difficult to secure." pages 363-364, (4802)

During the 1950's, Alton Ochsner wrote a brief monograph on lung cancer (See Chapter V). For two decades prior to its publication, Ochsner wrote on the subject. Although the articles were largely on the subject of surgical management of patients with lung cancer, Ochsner, DeBakey and their collaborators from Charity Hospital of New Orleans, reviewed etiology and clinical diagnosis. In publications between 1939 to 1948, Ochsner's changing opinion on causative role of cigarette smoking was reflected by the following quotations:

(3970) DeBakey & Ochsner

"The inhalation of irritating gases, such as war gas, exhaust gas of combustion motors, and gases arising from tarred roads, have been suggested as etiologic factors. The high incidence of carcinoma of the lung among workers in the Schneeberg mines has long been known. Investigations of these mines revealed that the air within these mines contained radio-active particles as well as a high content of arsenic and cobalt, and several investigators have expressed the opinion that the high incidence of primary lung malignancy among these mines is due to the radio-active factors. In a previous publication the authors have emphasized the possible etiologic relationship between the increase in smoking and the increase in pulmonary carcinoma. The irritating carcinogenic effects of tobacco have been repeatedly demonstrated. Roffo, on the basis of exten-

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sive clinical and experimental observation, concluded that tobacco is one of the most important carcinogenic agents, and has been able to produce tumors in rats experimentally as easily with tar obtained from tobacco as with coal tar. During the period, 1920-1936 inclusive, the authors observed a significant relationship between the increased incidence of cancer of the lung in the United States and the increased production of tobacco." pages 2524-2526, (3970)

Note: The cited article "In Press in Transactions of American Cancer Society" is not available to me after repeated attempts.

(3981) Ochsner & DeBakey

"Although it is controversial whether the increase in pulmonary carcinoma in recent years is apparent or real, the German autopsy statistics would indicate that the increase is actual and not only apparent. There are several explanations for the actual increase in the incidence of pulmonary malignancies, most of which have not been satisfactory. A number of theories have been suggested. Winternitz, Watson, and McNamara, because of the presence of metaplasia in the bronchial mucosa of persons dying from influenza, suggested that this change is a precancerous lesion. The inhalation of irritating gases such as war gas or gas originating from the increased use of motor cars has been proposed as an etiological factor. In our opinion the increase in smoking with the universal custom of inhaling is probably a responsible factor, as the inhaled smoke, constantly repeated over a long period of time, undoubtedly is a source of chronic irritation to the bronchial mucosa. In addition to the actual increase in pulmonary malignancy, there is unquestionably a relative increase in those localities where routine postmortem examinations previously have not been made. This is due probably to the fact that the condition has not been suspected in many cases and adequate diagnostic procedures have not been employed. The recent development of thoracic surgery has stimulated interest in intrathoracic lesions. This, with the development of specialized methods of diagnosis, has facilitated the recognition of pulmonary malignancies.

Summary: Chronic irritation of the bronchial mucosa is probably the most important etiological factor. Repeated inhalation of smoke over long periods of time is believed to be a prominent, irritating factor." pages 435-436, (3981)

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